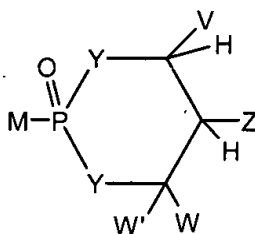


**We Claim:**

1. A compound of formula I:

**I**

*P*  
*not*  
*considered*  
*het atom*  
*all classification*

- 5 wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

- 10 together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

- 15 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

- 20 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkylthio, and aryloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

- 25 together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,

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-CHR<sup>2</sup>N<sub>3</sub>, -CH<sub>2</sub>aryl, -CH(aryl)OH, -CH(CH=CR<sup>2</sup>)OH, -CH(C≡CR<sup>2</sup>)OH, -R<sup>2</sup>, -NR<sup>2</sup>,  
 -OCOR<sup>3</sup>, -OCO<sub>2</sub>R<sup>3</sup>, -SCOR<sup>3</sup>, -SCO<sub>2</sub>R<sup>3</sup>, -NHCOR<sup>2</sup>, -NHCO<sub>2</sub>R<sup>3</sup>, -CH<sub>2</sub>NHaryl, -(CH<sub>2</sub>)<sub>p</sub>-  
 OR<sup>12</sup>, and -(CH<sub>2</sub>)<sub>p</sub>-SR<sup>12</sup>;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is -R<sup>2</sup>, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or  
 alicyclic;

R<sup>2</sup> is selected from the group consisting of R<sup>3</sup> and -H;

R<sup>3</sup> is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R<sup>6</sup> is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl,  
 alkoxycarbonyloxy alkyl and lower acyl;

R<sup>12</sup> is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-, -NR<sup>6</sup>- with the  
 proviso that at least one Y is -NR<sup>6</sup>-;

M is selected from the group that attached to PO<sub>3</sub><sup>2-</sup>, P<sub>2</sub>O<sub>6</sub><sup>3-</sup>, P<sub>3</sub>O<sub>9</sub><sup>4-</sup> or  
 P(O)(NHR<sup>6</sup>)O<sup>-</sup> is a biologically active agent but is not an FB Pase inhibitor, and is attached  
 to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not -NH(lower alkyl), -N(lower alkyl)<sub>2</sub>, -NH(lower alkylhalide),  
 -N(lower alkylhalide)<sub>2</sub>, or -N(lower alkyl)(lower alkylhalide); and

2) R<sup>6</sup> is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

2. The compounds of claim 1 wherein MP(O)(NHR<sup>6</sup>)O<sup>-</sup>, MPO<sub>3</sub><sup>2-</sup>, MP<sub>2</sub>O<sub>6</sub><sup>3-</sup>,  
 and MP<sub>3</sub>O<sub>9</sub><sup>4-</sup> is selected from the group consisting of an antiviral, anticancer,  
 antihyperlipidemic, antifibrotic, and antiparasitic agents.

3. The compound of claim 1 wherein MP(O)(NHR<sup>6</sup>)O<sup>-</sup>, MPO<sub>3</sub><sup>2-</sup>, MP<sub>2</sub>O<sub>6</sub><sup>3-</sup>, and  
 MP<sub>3</sub>O<sub>9</sub><sup>4-</sup> is selected from the group consisting of metalloprotease inhibitor, and TS  
 inhibitor.

4. The compounds of claim 2 wherein MH is selected from the group consisting of LdC, LdT, araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L-FddC, L-d4C, L-Fd4C, 3TC, ribavirin, penciclovir, 5-fluoro-2'-deoxyuridine, FIAU, FIAC, BHCG, 2'R,5'S(-)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine, (-)-b-L-2',3'-dideoxycytidine, (-)-b-L-2',3'-dideoxy-5-fluorocytidine, FMAU, BvaraU, E-5-(2-bromovinyl)-2'-deoxyuridine, Cobucavir, TFT, 5-propynyl-1-arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'-deoxyguanosine, Cytallene, Oxetanocin A, Oxetanocin G, Cyclobut A, Cyclobut G, fluorodeoxyuridine, dFdC, araC, bromodeoxyuridine, IDU, CdA, F-araA, 5-FdUMP, Coformycin, and 2'-deoxycoformycin.

5. The compounds of claim 2 wherein MH is selected from the group consisting of ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, and cytallene.

6. The compounds of claim 1 wherein  $\text{MPO}_3^{2-}$  is selected from the group consisting of PMEA, PMEDAP, HPMPC, HPMPA, FMPMA, and PMPA.

7. The compounds of claim 3 wherein M is attached to the phosphorus in formula I via an oxygen atom that is in a hydroxyl group on an acyclic sugar group.

8. The compounds of claim 7 wherein MH is selected from the group consisting of ACV, GCV, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine, and (R)-9-(3,4-dihydroxybutyl)guanine.

9. The compounds of claim 1 wherein M is attached to the phosphorus in formula I via a carbon atom.

10. The compounds of claim 9 wherein  $\text{M-PO}_3^{2-}$  is selected from the group consisting of phosphonoformic acid, and phosphonoacetic acid.

11. The compounds of claim 1 wherein  $\text{MP(O)(NH R}^6\text{)O}^-$ ,  $\text{MPO}_3^{2-}$ ,  $\text{MP}_2\text{O}_6^{3-}$ , or  $\text{MP}_3\text{O}_9^{4-}$  is useful for the treatment of diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product.

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alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus.

21. The compounds of claim 20 wherein V is selected from the group  
5 consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl; or  
together V and W are connected via an additional 3 carbon atoms to form a cyclic  
substituted group containing 6 carbon atoms and mono-substituted with a substituent  
selected from the group consisting of hydroxyl, acyloxy, alkoxycarbonyloxy,  
alkylthiocarbonyloxy, and aryloxycarbonyloxy attached to one of said additional carbon  
10 atoms that is three atoms from an Y attached to the phosphorus.

22. The compounds of claim 21 wherein V is selected from the group  
consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

23. The compounds of claim 22 wherein Z, W, and W' are H; and R<sup>6</sup> is  
15 selected from the group consisting of -H, and lower alkyl.

24. The compounds of claim 23 wherein V is selected from the group  
consisting of aryl and substituted aryl.

25. The compounds of claim 24 wherein V is selected from the group  
consisting of phenyl, and substituted phenyl.

26. The compounds of claim 25 wherein V is selected from the group  
25 consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, 3-  
bromophenyl, and 3,5-difluorophenyl.

27. The compounds of claim 22 wherein V is selected from the group  
consisting of heteroaryl and substituted heteroaryl.

28. The compounds of claim 27 wherein V is 4-pyridyl.

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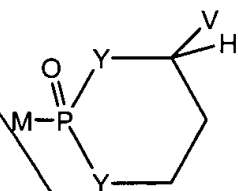
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Sub  
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37.

38. The compounds of claim 20 wherein said prodrug is a compound of formula VI:



VI

wherein

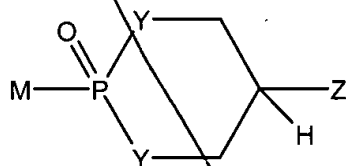
V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

39. The compounds of claim 38 wherein M is attached to phosphorus via an oxygen or carbon atom.

40. The compounds of claim 38 wherein V is selected from the group consisting of phenyl and substituted phenyl.

41. The compounds of claim 38 wherein V is selected from the group consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, and 4-pyridyl.

42. The compounds of claim 20 wherein said prodrug is a compound of formula VII:



VII

wherein

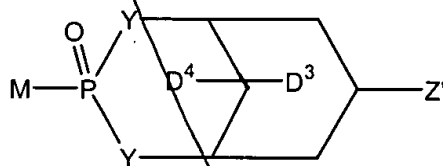
Z is selected from the group consisting of  
 $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  
 $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ , and  $-\text{CH}_2\text{aryl}$ .

43. The compounds of claim 42 wherein M is attached to the phosphorus via a carbon or oxygen atom.

44. The compounds of claim 43 wherein Z is selected from the group consisting of  
5  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC(O)R}^3$ , and  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ .

45. The compounds of claim 44 wherein  $\text{R}^2$  is  $-\text{H}$ .

10 46. The compounds of claim 20 wherein said prodrug is a compound of formula VIII:



VIII

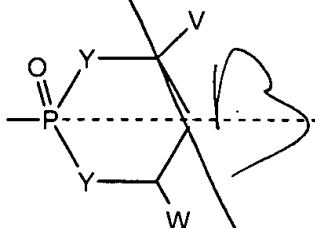
wherein

15  $\text{Z}'$  is selected from the group consisting of  $-\text{OH}$ ,  $-\text{OC(O)R}^3$ ,  $-\text{OCO}_2\text{R}^3$ , and  $-\text{OC(O)SR}^3$ ;

$\text{D}^3$  is  $-\text{H}$ ;

$\text{D}^4$  is selected from the group consisting of  $-\text{H}$ , alkyl,  $-\text{OH}$ , and  $-\text{OC(O)R}^3$ .

20 47. The compounds of claim 20 wherein  $\text{W}'$  and  $\text{Z}$  are  $-\text{H}$ ,  $\text{W}$  and  $\text{V}$  are both the same aryl, substituted aryl, heteroaryl, or substituted heteroaryl, and both  $\text{Y}$  groups are the same  $-\text{NR}^6-$ , such that the phosphonate prodrug moiety:



has a plane of symmetry through the phosphorus-oxygen double bond.

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48. The compounds of claim 32 wherein W and W' are H, V is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, and Z is selected from the group consisting of -H, OR<sup>2</sup>, and -NHCOR<sup>2</sup>.

49. The compounds of claim 48 wherein Z is -H, and M is attached to the phosphorus of formula I via an oxygen or carbon atom.

50. The compounds of claim 49 wherein V is selected from the group consisting of phenyl or substituted phenyl.

51. The compounds of claim 49 wherein V is an optionally substituted monocyclic heteroaryl containing at least one nitrogen atom.

52. The compounds of claim 49 wherein M is attached via an oxygen atom.

53. The compounds of claim 51 wherein V is 4-pyridyl.

54. The compounds of claim 52 wherein MH is selected from the group consisting of LdC, LdT, araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L-FddC, L-d4C, L-Fd4C, 3TC, ribavirin, penciclovir, 5-fluoro-2'-deoxyuridine, FIAU, FIAC, BHCG, 2'R,5'S(-)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine, (-)-b-L-2',3'-dideoxycytidine, (-)-b-L-2',3'-dideoxy-5-fluorocytidine, FMAU, BvaraU, E-5-(2-bromovinyl)-2'-deoxyuridine, Cobucavir, TFT, 5-propynyl-1-arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'-deoxyguanosine, Cytallene, Oxetanocin A, Oxetanocin G, Cyclobut A, Cyclobut G, fluorodeoxyuridine, dFdC, araC, bromodeoxyuridine, IDU, CdA, F-ara-A, 5-FdUMP, coformycin, and 2'-deoxycycoformycin.

55. The compounds of claim 52 wherein MH is selected from the group consisting of ACV, GCV, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine, and (R)-9-(3,4-dihydroxybutyl)guanine.

57. The compounds of claim 56 wherein V is selected from the group consisting of phenyl and 4-pyridyl and MH is selected from the group consisting of PMEA, PMEDAP, HPMPC, HPMMA, FPMMA, and PMMA.

Chemical structure diagram showing a metal-oxaphosphorinane complex. The central phosphorus atom (P) is double-bonded to an oxygen atom (O) and single-bonded to a metal atom (M). The phosphorus atom is also bonded to two Y atoms and two carbon atoms of a five-membered ring. The ring carbons are also bonded to V, H, Z, W, and W' atoms.

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy,

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with the provisos that:

b) when Z is  $-R^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or aralkenyl;

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R<sup>6</sup> is selected from the group consisting of -H, lower alkyl, acyloxyalkyl,

R<sup>12</sup> is selected from the group consisting of -H, and lower acyl;

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$\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FB Pase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not  $\text{-NH(lower alkyl)}$ ,  $\text{-N(lower alkyl)}_2$ ,  $\text{-NH(lower alkylhalide)}$ ,

2)  $R^6$  is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

59. The method of claim 58 wherein M is attached to the phosphorus in formula I via an oxygen atom; wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H or alkyl;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl.

60. The method of claim 59 wherein MH or  $\text{MPO}_3^{2-}$  is selected from the group consisting of LdC, LdT, araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl)-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC, araC, bromodeoxyuridine, IDU, CdA,

FaraA, Coformycin, 2'-deoxycoformycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6  
 5 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxycytidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, and cytallene.

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61. The method of claim 58 wherein  $\text{MPO}_3^{2-}$  is selected from the group consisting of PMEA, PMEDAP, HPMPC, HPMPA, FMPMA, and PMPA.

62. The method of claim 58 wherein  $\text{MPO}_3^{2-}$ ,  $\text{MP}_2\text{O}_6^{3-}$ , or  $\text{MP}_3\text{O}_9^{4-}$  is useful for the treatment of diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product.

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63. The method of claim 62 wherein said disease of the liver is selected from the group consisting of diabetes, hepatitis, cancer, fibrosis, malaria, gallstones, and chronic cholecystalithiasis.

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64. The methods of claim 63 wherein  $\text{MPO}_3^{2-}$ ,  $\text{MP}_2\text{O}_6^{3-}$ , or  $\text{MP}_3\text{O}_9^{4-}$  is an antiviral or anticancer agent.

65. The method of claim 62 wherein said metabolic disease is selected from the group consisting of diabetes, atherosclerosis, and obesity.

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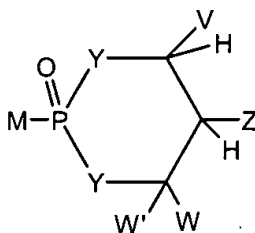
66. The method of claim 62 wherein said biochemical end product is selected from the group consisting of glucose, cholesterol, fatty acids, and triglycerides.

67. The method of claim 66 wherein  $\text{MPO}_3^{2-}$  is an AMP activated protein kinase activator.

68. The method of claim 58 wherein said oral bioavailability is at least 10%.

69. The method of claim 58 wherein said oral bioavailability is enhanced by 50% compared to the parent drug administered orally.

70. A method of delivering a biologically active drug to an animal for a sustained period using compounds of formula I:



# I

10 wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group  
15 containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,  
alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms  
from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, carbonyloxy, alkylthiocarbonyloxy, and aryloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

5 Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p$ - $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p$ - $\text{SR}^{12}$ ;

p is an integer 2 or 3;

10 with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

15  $\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxy carbonyloxy alkyl and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

20 each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the proviso that at least one Y is  $-\text{NR}^6$ -;

M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or

$\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

25 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and

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- 2)  $R^6$  is not lower alkylhalide;  
and pharmaceutically acceptable prodrugs and salts thereof.

71. The method of claim 70 wherein M is attached to the phosphorus in  
5 formula I via an oxygen atom or a carbon atom; wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one  
10 substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or  
15 substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p$ -  
20  $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{-SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and  
b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H or alkyl;  
25  $\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;  
 $\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;  
 $\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl.

72. The method of claim 71 wherein MH or  $\text{MPO}_3^{2-}$  is selected from the group  
30 consisting of LdC, LdT, araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L-FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FIAU, FIAC, BHCG, L-FMAU, BvaraU, E-5-(2-bromovinyl)-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A,

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oxetanocin G, Cyclobut A, Cyclobut G, dFdC, araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycoformycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxycytidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene

PMEA, PMEDAP, HPMPC, HPMPA, FPMPA, PMPA, foscarnet, and phosphonoformic acid.

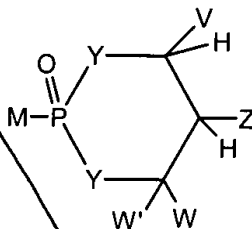
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73. The method of claim 70 whereby therapeutic levels of said drug are maintained for at least one hour longer than the levels achieved by oral administration of the bispivaloyloxymethyl (bis-POM) ester.

15

74. The method of claim 70 wherein MH or  $\text{MPO}_3^{2-}$  is an antiviral or anticancer agent.

75. A method of delivering a biologically active drug to an animal with greater selectivity for the liver using compounds of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

25

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,

alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the proviso that at least one Y is  $-\text{NR}^6$ -;

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M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or  $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom; with the provisos that:

- 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and
- 2)  $\text{R}^6$  is not lower alkylhalide;
- and pharmaceutically acceptable prodrugs and salts thereof.

10

76. The method of claim 75 whereby the ratio of a parent drug or a drug metabolite concentration in the liver over a parent drug or a drug metabolite concentration in the plasma is two times greater compared to administration of a parent drug.

15

77. The method of claim 76 wherein the liver specificity has increased relative to administration of  $\text{M-PO}_3^{2-}$ .

20

78. The method of claim 75 wherein said biologically active drug is a triphosphate generated in the liver.

25

79. The method of claim 78 wherein MH is selected from the group consisting of araA, AZT, d4T, 3TC, 1- $\beta$ -D-ribofuranosyl-1,2,4-triazole-3-carboxamide, ACV, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine, 5-yl-carbocyclic 2'-deoxyguanosine, dFdC, araC, F-ara-A, FTC, and CdA.

80. The method of claim 75 wherein the active drug is  $\text{MPO}_3^{2-}$ .

81. The method of claim 80 wherein the drug is selected from the group consisting of FdUMP.

30

82. The method of claim 75 wherein the active drug is  $\text{MP}_3\text{O}_9^{4-}$  and M is attached via carbon.

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Chemical structure showing a substituted cyclohexane ring. The ring is connected to a phosphorus atom (P) which is double-bonded to an oxygen atom (O) and single-bonded to a metal atom (M). The ring has substituents V, H, Z, H, W, and W' at different positions.

# I

10 V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

15    alkoxy-carbonyloxy, or aryloxy-carbonyloxy attached to a carbon atom that is three atoms  
from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

20 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

25            together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  
 5  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  
 $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  
 $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p$ -  
 $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p$ - $\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

10 *Sup Blue*  
 a) V, Z, W, W' are not all -H; and  
 b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or  
 alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

15  $\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl,  
 alkoxy carbonyloxy alkyl and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the  
 20 proviso that at least one Y is  $-\text{NR}^6$ -;

M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or  
 $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is  
 attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

25 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  
 $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and

2)  $\text{R}^6$  is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

30 85. The method of claim 84 wherein extrahepatic toxicity is reduced.

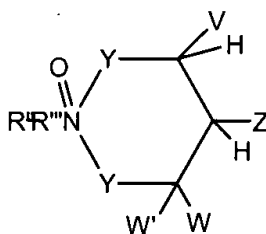
86. The method of claim 85 wherein  $\text{M-PO}_3^{2-}$  is excreted by the kidney.

87. The method of claim 85 wherein the gastrointestinal toxicity is reduced.

88. The method of claim 85 wherein central or peripheral nervous system toxicity is reduced.

5

89. A method of bypassing kinase resistance by administering to an animal compounds of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkylthio, and aryloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

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5 together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

10

with the provisos that:

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R<sup>3</sup> is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R<sup>6</sup> is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl,

each Y is independently selected from the group consisting of -O-, -NR<sup>6</sup>- with the proviso that at least one Y is -NR<sup>6</sup>-;

M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or

with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)<sub>2</sub>, -NH(lower alkylhalide),  
 ver alkylhalide)<sub>2</sub>, or -N(lower alkyl) (lower alkylhalide); and

- 2)  $R^6$  is not lower alkylhalide;  
and pharmaceutically acceptable prodrugs and salts thereof.

90. The method of claim 89 wherein said resistance arises from the absence or low levels of enzymes responsible for phosphorylating MH.

91. The method of claim 89 wherein said resistance arises from inadequate  
5 cellular production of  $M-PO_3^{2-}$ .

92. The method of claim 89 wherein said compound is an anticancer or antiviral agent.

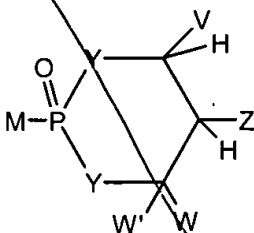
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93. The method of claim 92 wherein MH is F-ara-A, araC, CdA, dFdC, and 5-fluoro-2'-deoxyuridine.

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94. The method of claim 92 wherein said resistance is to an antiviral agent selected from the group consisting of LdC, LdT, araA, AZT, d4T, 3TC, ribavirin, 5 fluoro-  
15 2'-deoxyuridine, FMAU, DAPD, FTC, 5-yl-carbocyclic 2'-deoxyguanosine, Cyclobut G, dFdC, araC, IDU, FaraA, ACV, GCV, DXG, and penciclovir.

95. The method of claim 92 wherein the resistance or lack of antihepatitis activity is due to a deficiency in thymidine kinase and said antiviral agent is selected from  
20 the group consisting of AZT, d4T, and ACV.

96. The method of claim 92 wherein said anticancer agent is selected from the group consisting of dFdC, araC, F-araA, and CdA.

25 97. A method of treating cancer expressing a P450 enzyme, by administering to an animal a compound of formula I:



I



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

5       together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

10       together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

15       together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

20       together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

20       together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

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Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p-$   
 5  $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p-\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or  
 10 alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl,  
 alkoxy-carbonyloxy alkyl and lower acyl;

15  $\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the  
 proviso that at least one Y is  $-\text{NR}^6$ -;

M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or  
 $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is  
 20 attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;  
 with the provisos that:

1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  
 $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and

2)  $\text{R}^6$  is not lower alkylhalide;

25 and pharmaceutically acceptable prodrugs and salts thereof.

98. The method of claim 97 wherein said cancer is hepatocellular carcinoma.

99. The method of claim 97 wherein the active drug is the triphosphate of M-H.

30.

100. The method of claim 97 wherein the active drug is the monophosphate of  
 M-H.

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101. The method of claim 97 wherein said prodrug is administered to patients resistant to the parent drug.

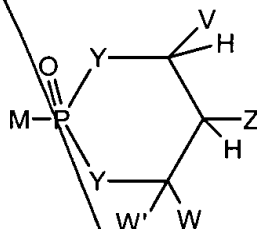
102. The compounds of claim 1 wherein R<sup>6</sup> is lower alkyl.

103. The compounds of claim 102 wherein R<sup>6</sup> is methyl.

104. The method of claim 100 wherein MH is selected from the group consisting of F-araA, araC, CdA, dFdc, and 5-fluoro-2'-deoxyuridine.

105. The method of claim 97 wherein MH is selected from the group consisting of dFdC, araC, FaraA, CdA, 5-fluoro 2'deoxyuridine, GCV, tiazofurin, IDU, 5,6 dihydro-5-azacytidine, 5-azacytidine, and 5-aza 2'deoxycytidine.

106. A method of treating liver fibrosis by administering to an animal a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, or attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

5 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

10 together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

15 Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{SR}^{12}$ ;

20 p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

25  $\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

30 each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the proviso that at least one Y is  $-\text{NR}^6$ -;

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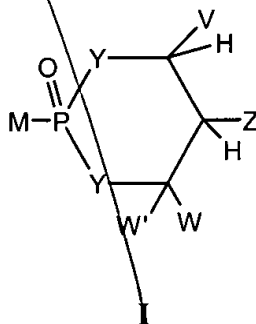
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M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or

$\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom; with the provisos that:

- 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and
  - 2)  $\text{R}^6$  is not lower alkylhalide;
- and pharmaceutically acceptable prodrugs and salts thereof.

107. A method of treating hyperlipidemia by administering to an animal a compound of formula I:



wherein:

- V, W, and W' are independently selected from the group consisting of  $-\text{H}$ , alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, or attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

- together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy;

5

Sub

10

$p$  is an integer 2 or 3;

15

a)  $V, Z, W, W'$  are not all  $-H$ ; and

b) when Z is  $-R^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or

$R^2$  is selected from the group consisting of  $R^3$  and  $-H$ ;

20

R<sup>6</sup> is selected from the group consisting of H, and lower alkyl, acyloxyalkyl,

carbonyloxy alkyl and lower acyl;

R<sup>12</sup> is selected from the group consisting of -H, and lower acyl;

25

M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or

THR<sup>6</sup>)O<sup>-</sup> is a biologically active agent, but is not an FBPase inhibitor, and is bound to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom.

with the provisos that:

30

2)  $R^6$  is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

The method of claim 107 wherein the inhibitor:

A method of treating parasitic infection of formula I:

I

, and W' are independently selected from cyclic, aryl, substituted aryl, heteroaryl, s

her V and Z are connected via an addition-7 ring atoms, optionally 1 heteroatom, snyloxy, or aryloxycarbonyloxy attached groups attached to the phosphorus; or

her V and Z are connected via an addition-containing 1 heteroatom, said cyclic group position to the Y adjacent to V;

her V and W are connected via an addition-substituted cyclic group containing 6 carbselected from the group consisting of hydonyloxy, and aryloxycarbonyloxy, attacthree atoms from a Y attached to the ph

her Z and W are connected via an addition-containing one heteroatom, and Y must be

5



V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

10

15

20

25

sub  
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together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  
 5  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  
 $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  
 $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p-$   
 $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p-\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and  
 b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

15  $\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxy carbonyloxy alkyl and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6-$  with the  
 20 proviso that at least one Y is  $-\text{NR}^6-$ ;

M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or

$\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 25 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  
 $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and

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$R^6$  is not lower alkylhalide;

5 administration to an animal of compound of formula I:



10 wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

15 containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group,  
optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta  
20 and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

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together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  
 5  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  
 $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  
 $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p$ -  
 $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{-SR}^{12}$ ;

p is an integer 2 or 3;

10 with the provisos that:

- a) V, Z, W, W' are not all -H; and  
 b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxy carbonyloxy alkyl and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the  
 20 proviso that at least one Y is  $-\text{NR}^6$ -;

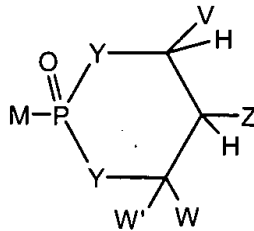
M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or  
 $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is  
 attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

- 25 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  
 $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and  
 2)  $\text{R}^6$  is not lower alkylhalide;  
 and pharmaceutically acceptable prodrugs and salts thereof.

30 111. The method of claim 110 wherein MH is IDU.

112. A method of treating viral infections by administering to an animal a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkoxy, alkylthiocarbonyloxy, and aryloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

- Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  
 $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  
 $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  
 $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p$ -  
 5  $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p$ - $\text{SR}^{12}$ ;  
 p is an integer 2 or 3;  
 with the provisos that:  
 a) V, Z, W, W' are not all -H; and  
 b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or  
 10 alicyclic;  
 $\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;  
 $\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;  
 $\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl,  
 alkoxy carbonyloxy alkyl and lower acyl;  
 15  $\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;  
 each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the  
 proviso that at least one Y is  $-\text{NR}^6$ -;  
 M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$  or  
 $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is  
 20 attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;  
 with the provisos that:  
 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,  
 $-\text{N}(\text{lower alkylhalide})_2$ , or  $-\text{N}(\text{lower alkyl})(\text{lower alkylhalide})$ ; and  
 2)  $\text{R}^6$  is not lower alkylhalide;  
 25 and pharmaceutically acceptable prodrugs and salts thereof.

113. The method of claim 112 wherein said viral infection is hepatitis.

114. The method of claim 113 wherein MH is selected from the group consisting  
 30 of lobucovir, FTC, 3TC, BMS 200,475, DAPD, DXG, L-FMAU, LdC, LdT, ribavirin,  
 ACV, GCU, and pencyclovir.

115. The method of claim 113 wherein said prodrug is administered to patients resistant to the parent drug.

116. The method of claim 112 wherein said hepatitis is hepatitis B.

117. The method of claim 112 wherein said hepatitis is hepatitis C.

118. The methods of claim 112 wherein viral kinases produce  $M-PO_3^{2-}$ .

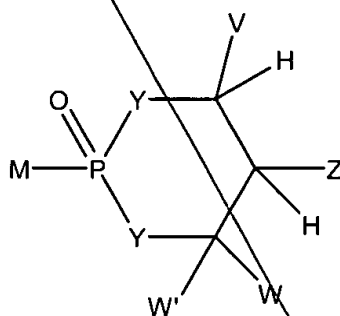
119. The method of claim 118 wherein said viral infection is hepatitis and said viral kinases are kinases from viruses other than the hepatitis viruses.

120. The method of claim 112 wherein the active drug is the triphosphate of M-H.

121. A method of delivering a biologically active drug to target tissues comprising:

a) enhancing the activity of a P450 enzyme that oxidizes the compounds of formula I in said target tissues; and

b) administering to an animal a compound of formula I:



I

wherein:

together V and Z are connected via an additional 3-5 atoms to form a cyclic group  
5 containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,  
alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms  
from both Y groups attached to the phosphorus; or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

$p$  is an integer 2 or 3;

with the provisos that:

30 a) V, Z, W, W' are not all -H; and  
b) when Z is -R<sup>2</sup>, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$R^2$  is selected from the group consisting of  $R^3$  and  $-H$ ;

R<sup>3</sup> is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$R^6$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxy-carbonyloxyalkyl, and lower acyl;

$R^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-, -NR<sup>6</sup>- with the proviso that at least one Y is -NR<sup>6</sup>-;

M is selected from the group that attached to PO<sub>3</sub><sup>2-</sup>, P<sub>2</sub>O<sub>6</sub><sup>3-</sup>, P<sub>3</sub>O<sub>9</sub><sup>4-</sup>, or

P(O)(NHR<sup>6</sup>)O<sup>-</sup> is a biologically active agent, but is not an FB Pase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

with the provisos that:

1) M is not -NH(lower alkyl), -N(lower alkyl)<sub>2</sub>, -NH(lower alkylhalide), -N(lower alkylhalide)<sub>2</sub>, or -N(lower alkyl) (lower alkylhalide); and

2) R<sup>6</sup> is not lower alkylhalide;

and pharmaceutically acceptable prodrugs and salts thereof.

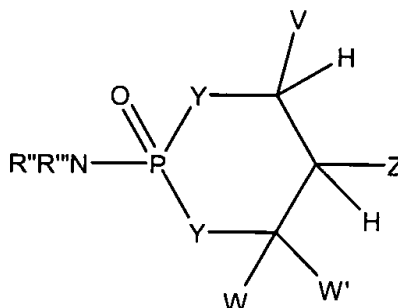
122. The method of claim 121 wherein the activity of a P450 enzyme is enhanced by administering genes that encode a P450 enzyme.

123. The method of claim 121 wherein said activity of P450 enzymes is enhanced by delivering to said target tissue, cells engineered to express P450 enzymes.

124. The method of claim 121 wherein said P450 enzyme activity is enhanced by administration of a compound that increases the amount of endogenous P450 enzyme.

125. The method of claim 124 wherein said compound that increases the amount of endogenous P450 enzyme is selected from the group consisting of phenobarbital, dexamethasone, rifampicin, phenytoin, and pregnanolon-16 $\alpha$ -carbonitrile.

126. A method of treating tumor cells expressing a P450 enzyme comprising administering a cyclophosphamide analog selected from the group consisting of



wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl,  
5 aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group  
containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,  
alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms  
10 from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group,  
optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta  
and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an  
15 optionally substituted cyclic group containing 6 carbon atoms and substituted with one  
substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy,  
alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon  
atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group,  
20 optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or  
substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic  
group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl,  
heteroaryl, or substituted heteroaryl;

25 Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  
 $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,

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-CHR<sup>2</sup>N<sub>3</sub>, -CH<sub>2</sub>aryl, -CH(aryl)OH, -CH(CH=CR<sup>2</sup>)OH, -CH(C≡CR<sup>2</sup>)OH, -R<sup>2</sup>, -NR<sup>2</sup>,  
 -OCOR<sup>3</sup>, -OCO<sub>2</sub>R<sup>3</sup>, -SCOR<sup>3</sup>, -SCO<sub>2</sub>R<sup>3</sup>, -NHCOR<sup>2</sup>, -NHCO<sub>2</sub>R<sup>3</sup>, -CH<sub>2</sub>NHaryl, -(CH<sub>2</sub>)<sub>p</sub>-  
 OR<sup>12</sup>, and -(CH<sub>2</sub>)<sub>p</sub>-SR<sup>12</sup>;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is -R<sup>2</sup>, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or  
 alicyclic;

R<sup>2</sup> is selected from the group consisting of R<sup>3</sup> and -H;

R<sup>3</sup> is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R<sup>66</sup> is selected from the group consisting of -H, lower 2-haloalkyl, and lower alkyl;

R<sup>12</sup> is selected from the group consisting of -H, and lower acyl;

R'' is lower 2-haloalkyl;

R''' is selected from the group consisting of H, lower alkyl, and R'';

each Y is independently selected from the group consisting of -O-, -NR<sup>66</sup>- with the  
 proviso that at least one Y is -NR<sup>66</sup>-;

and pharmaceutically acceptable prodrugs and salts thereof.

127. The method of claim 126 wherein said tumor cell is hepatocellular  
 carcinoma.

128. The method of claim 127 wherein R'' is 2-chloroethyl, and R''' is selected  
 from the group consisting of -H, and 2-chloroethyl.

129. The method of claim 127 wherein R<sup>66</sup> is selected from the group consisting  
 of -H, CH<sub>3</sub>, and 2-chloroethyl.

130. The method of claim 127 wherein Z, W, W', and R<sup>66</sup> are -H, and R'' and  
 R''' are 2-chloroethyl.

131. The method of claim 127 wherein the activity of a P450 enzyme is  
 enhanced by administration of a compound that increases the amount of endogenous P450  
 enzyme.

132. The method of claim 131 wherein said compound that increases the amount of endogenous P450 enzyme is selected from the group consisting of phenobarbitol, dexamethasone, rifampicin, phenytoin, and preganolon-16 $\alpha$ -carbonitrile.

5 133. The method of claim 126 wherein V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

10 134. The method of claim 133 wherein Z, W, W', and R<sup>66</sup> are -H, and R'' and R''' are 2-chloroethyl.

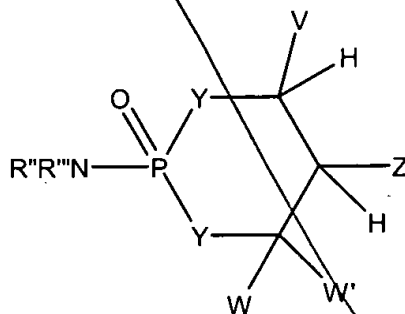
135. The method of claim 133 wherein R'', Z, W, and W' are -H, and R'' and R<sup>66</sup> are 2-chloroethyl.

15 136. The method of claim 133 wherein V is selected from the group consisting of phenyl, 3-chlorophenyl, and 3 bromophenyl.

137. The method of claim 133 wherein V is 4-pyridyl.

20 138. A method of treating tumor cells comprising

- a) enhancing the activity of a P450 enzyme that oxidizes cyclophosphamide analogs;
- b) administering to an animal a cyclophosphamide analog selected from the group consisting of:



25

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

5 together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

10 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

15 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

20 together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

25 Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

30 a) V, Z, W, W' are not all -H; and  
b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

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$R^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$R^{66}$  is selected from the group consisting of -H, lower 2-haloalkyl, and lower alkyl;

$R^{12}$  is selected from the group consisting of -H, and lower acyl;

$R''$  is lower 2-haloalkyl;

$R'''$  is selected from the group consisting of H, lower alkyl, and  $R''$ ;

each Y is independently selected from the group consisting of -O-,  $-NR^{66}$ - with the proviso that at least one Y is  $-NR^{66}$ -;

and pharmaceutically acceptable prodrugs and salts thereof.

10 139. The method of claim 138 wherein the activity of a P450 enzyme is enhanced by administering genes that encode a P450 enzyme.

140. The method of claim 138 wherein said activity of a P450 enzyme is enhanced by delivering to a tumor, cells engineered to express a P450 enzyme.

15 141. The method of claim 138 wherein said P450 enzyme activity is enhanced by administration of a compound that increases the amount of endogenous P450 enzyme.

20 142. The method of claim 141 wherein said compound that increases the amount of endogenous P450 enzyme is selected from the group consisting of phenobarbital, dexamethasone, rifampicin, phenytoin, and preganolon-16 $\alpha$ -carbonitrile.

25 143. The method of claim 138 wherein  $R''$  is 2-chloroethyl, and  $R'''$  is selected from the group consisting of -H, and 2-chloroethyl.

144. The method of claim 138 wherein  $R^{66}$  is selected from the group consisting of -H,  $CH_3$ , and 2-chloroethyl.

30 145. The method of claim 138 wherein V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

146. The method of claim 145 wherein Z, W, W', and  $R^{66}$  are -H, and  $R''$  and  $R'''$  are 2-chloroethyl.

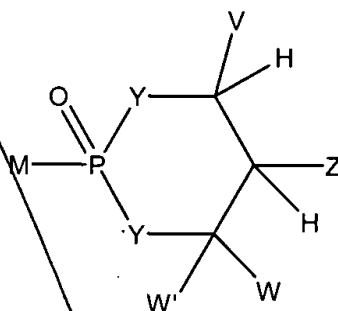
147. The method of claim 145 wherein Z, W, W', and R''' are -H, and R'' and R<sup>66</sup> are 2-chloroethyl.

148. The method of claim 145 wherein V is selected from the group consisting of phenyl, 3-chlorophenyl, and 3 bromophenyl.

149. The method of claim 145 wherein V is 4-pyridyl.

150. A method of making a prodrug of a compound drug having a -PO<sub>3</sub><sup>2-</sup> or -P(O)(NHR<sup>6</sup>)O<sup>-</sup> moiety comprising,

a) transforming said phosph(on)ate into a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

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together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}=\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^6-$  with the proviso that at least one Y is  $-\text{NR}^6-$ ;

M is selected from the group that attached to  $\text{PO}_3^{2-}$ ,  $\text{P}_2\text{O}_6^{3-}$ ,  $\text{P}_3\text{O}_9^{4-}$ , or  $\text{P}(\text{O})(\text{NHR}^6)\text{O}^-$  is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom; with the provisos that:

- 1) M is not  $-\text{NH}(\text{lower alkyl})$ ,  $-\text{N}(\text{lower alkyl})_2$ ,  $-\text{NH}(\text{lower alkylhalide})$ ,

~~-N(lower alkylhalide)<sub>2</sub>, or -N(lower alkyl) (lower alkylhalide); and~~

~~2) R<sup>6</sup> is not lower alkylhalide;  
and pharmaceutically acceptable prodrugs and salts thereof.~~

5 151. The method of claim 150 further comprising,  
a) converting M-PO<sub>3</sub><sup>2-</sup> to a compound M-P(O)L''<sub>2</sub> wherein L'' is a leaving  
group selected from the group consisting of halogen; and  
b) reacting M-P(O)L''<sub>2</sub> with HY-CH(V)CH(Z)CH(Z)-CW(W')-YH.

10 152. The method of claim 151 wherein HY-CH(V)CH(Z)-CW(W')-YH is chiral.

153. The method of claim 152 further comprising isolating a single  
diastereomer.

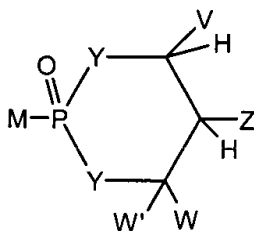
15 154. The method of claim 150 wherein  
a) converting a hydroxyl or amino to a phosphoramidite by reaction with L-  
P(-YCH(V)CH(Z)-CW(W')Y-) wherein L selected from the group consisting of NR<sup>1</sup><sub>2</sub>, and  
halogen; and  
b) transforming said phosphoramidite into a compound of formula I by  
20 reaction with an oxidizing agent.

~~155. The method of claim 154 wherein L-P(-YCH(V)CH(Z)-CW(W')Y-) is  
chiral.~~

25 156. The method of claim 155 wherein the chiral phosphoramidite is generated  
using a chiral amino alcohol.

157. The method of claim 155 wherein said oxidizing agent produces a single  
stereoisomer at the phosphorus.

158. The method of making a prodrug of formula I:



I

5 comprising converting a hydroxyl or an amino to a phosphate or phosphoramidate, respectively, by reaction with  $L'-P(O)(-YCH(V)CH(Z)-CW(W')Y-)$

wherein  $L'$  is a leaving group selected from the group consisting of  $-NR^2$ , aryloxy, and halogen;

10 V, W, and  $W'$  are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

20 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkoxy, alkylthiocarbonyloxy, and aryloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

25 together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

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together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC(O)R}^3$ ,  
 5  $-\text{CHR}^2\text{OC(S)R}^3$ ,  $-\text{CHR}^2\text{OC(S)OR}^3$ ,  $-\text{CHR}^2\text{OC(O)SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  
 $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH(aryl)OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  
 $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p$ -  
 $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p$ - $\text{SR}^{12}$ ;

p is an integer 2 or 3;

10 with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

15  $\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxy carbonyloxyalkyl, and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

20 each Y is independently selected from the group consisting of  $-\text{O}-$ ,  $-\text{NR}^6-$  with the proviso that at least one Y is  $-\text{NR}^6-$ .

159. The method of claim 158 wherein  $\text{L}'\text{-P(O)}(-\text{YCH(V)CH(Z)-CW(W')Y-})$  is a single stereoisomer.

25 160. The method of claim 159 wherein said stereoisomer is generated using a chiral amino alcohol.

161. A compound,

$\text{R}^1_2\text{N-P-}(-\text{YCH(V)CH(Z)-CW(W')Y-})$

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

5 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one  
10 substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or  
15 substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  
20  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  
 $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  
 $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^3$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{SR}^{12}$ ;

p is an integer 2 or 3;

25 q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

30 each  $\text{R}^1$  is independently selected from the group consisting of alkyl, aryl, and aralkyl or together  $\text{R}^1$  and  $\text{R}^1$  form a cyclic group, optionally containing a heteroatom;

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$R^2$  is selected from the group consisting of  $R^3$  and -H;

$R^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$R^6$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl, alkoxy-carbonyloxyalkyl, and lower acyl;

$R^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is selected from the group consisting of -O- and -NR<sup>6</sup>- with the proviso that at least one Y is -NR<sup>6</sup>-.

with the proviso that  $R^1$  is not methyl.

10 162. A compound  $R^1_2N-P(O)(-YCH(V)CH(Z)-CW(W')Y-)$

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

15 together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy-carbonyloxy, or aryloxy-carbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

20 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

25 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy-carbonyloxy, alkylthio-carbonyloxy, and aryloxy-carbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

30 together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of -CHR<sup>2</sup>OH, -CHR<sup>2</sup>OC(O)R<sup>3</sup>,

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$-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  
 $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  
 $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p-$   
 $\text{OR}^{12}$ , and  $-(\text{CH}_2)_p-\text{SR}^{12}$ ;

5 p is an integer 2 or 3;

q is an integer 1 or 2;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or  
 10 alicyclic;

each  $\text{R}^1$  is independently selected from the group consisting of alkyl, aryl, and  
 aralkyl;

or together  $\text{R}^1$  and  $\text{R}^1$  form a cyclic group, optionally containing a heteroatom;

with the proviso that both  $\text{R}^1$  groups are not benzyl or ethyl at the same time; and

15  $\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

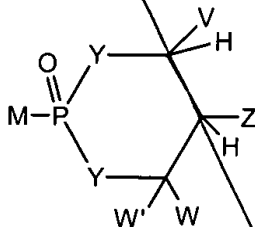
$\text{R}^6$  is selected from the group consisting of -H, lower alkyl, acyloxyalkyl,  
 alkoxy-carbonyloxyalkyl, and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

20 each Y is selected from the group consisting of -O- and  $-\text{NR}^6$ - with the proviso  
 that at least one Y is  $-\text{NR}^6$ -.

163. A method of delivering a compound to hepatocytes wherein said compound  
 has a moiety selected from the group consisting of phosph(on)ate comprising:

25 a) converting said compound to a prodrug of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

5 together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, alkoxy, or aryloxy, alkoxy, or aryloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

10 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkoxy, alkylthio, alkoxy, and aryloxy, alkoxy, or aryloxy attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

15 together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

20 together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

25 Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{OR}^{12}$ , and  $-(\text{CH}_2)_p\text{SR}^{12}$ ;

p is an integer 2 or 3;

with the provisos that:

- 30 a) V, Z, W, W' are not all -H; and  
b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

$\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$R^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxy-carbonyloxy alkyl and lower acyl;

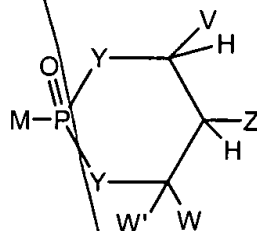
$R^{12}$  is selected from the group consisting of -H, and lower acyl;

each Y is independently selected from the group consisting of -O-, -NR<sup>6</sup>- with the proviso that at least one Y is -NR<sup>6</sup>-;

M is selected from the group that attached to PO<sub>3</sub><sup>2-</sup>, P<sub>2</sub>O<sub>6</sub><sup>3-</sup>, P<sub>3</sub>O<sub>9</sub><sup>4-</sup> or P(O)(NHR<sup>6</sup>)O<sup>-</sup> is a biologically active agent, but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom; with the provisos that:

- 1) M is not -NH(lower alkyl), -N(lower alkyl)<sub>2</sub>, -NH(lower alkylhalide), -N(lower alkylhalide)<sub>2</sub>, or -N(lower alkyl) (lower alkylhalide); and
  - 2)  $R^6$  is not lower alkylhalide;
- and pharmaceutically acceptable prodrugs and salts thereof.

164. A method of enhancing the pharmacodynamic half-life of a parent drug by administering to an animal a prodrug of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy-carbonyloxy, or aryloxy-carbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V;

together V and W are connected via an additional 3 carbon atoms to form an  
 5 optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said additional carbon atoms that is three atoms from a Y attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group,  
 10 optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

15 Z is selected from the group consisting of  $-\text{CHR}^2\text{OH}$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$ ,  $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$ ,  $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$ ,  $-\text{CHR}^2\text{OCO}_2\text{R}^3$ ,  $-\text{OR}^2$ ,  $-\text{SR}^2$ ,  $-\text{CHR}^2\text{N}_3$ ,  $-\text{CH}_2\text{aryl}$ ,  $-\text{CH}(\text{aryl})\text{OH}$ ,  $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$ ,  $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$ ,  $-\text{R}^2$ ,  $-\text{NR}^2_2$ ,  $-\text{OCOR}^3$ ,  $-\text{OCO}_2\text{R}^3$ ,  $-\text{SCOR}^3$ ,  $-\text{SCO}_2\text{R}^3$ ,  $-\text{NHCOR}^2$ ,  $-\text{NHCO}_2\text{R}^3$ ,  $-\text{CH}_2\text{NHaryl}$ ,  $-(\text{CH}_2)_p\text{-OR}^{12}$ , and  $-(\text{CH}_2)_p\text{-SR}^{12}$ ;

20 p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is  $-\text{R}^2$ , then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

25  $\text{R}^2$  is selected from the group consisting of  $\text{R}^3$  and -H;

$\text{R}^3$  is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

$\text{R}^6$  is selected from the group consisting of -H, and lower alkyl, acyloxyalkyl, alkoxycarbonyloxy alkyl and lower acyl;

$\text{R}^{12}$  is selected from the group consisting of -H, and lower acyl;

30 each Y is independently selected from the group consisting of -O-,  $-\text{NR}^6$ - with the proviso that at least one Y is  $-\text{NR}^6$ -;

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- 10            165.    The compounds of claim 1 wherein V and M are *cis* to one another on the  
ring of the prodrug.

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